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Associations of acetylcholinesterase inhibitor treatment with reduced mortality in Alzheimer's disease: A retrospective survival analysis

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Abstract

Background: Dementia is increasingly recognised as life-limiting condition. Although the benefits of acetylcholinesterase inhibitors (AChEIs) on cognition and function are well established, their effect on survival is less clear.

Objective: To investigate associations between AChEI prescription and mortality in patients with Alzheimer's dementia in a naturalistic setting, using detailed baseline data on cognition, functioning, and mental and physical wellbeing.

Methods: We used a large mental health care database in South London, linked to Hospital Episode Statistics and Office for National Statistics mortality data, to assemble a retrospective cohort. We conducted a survival analysis adjusting for a wide range of potential confounders using propensity scores to reduce the impact of confounding by indication.

Results: Of 2464 patients with Alzheimer's disease, 1261 were prescribed AChEIs. We detected a strong association between AChEI receipt and lower mortality (hazard ratio=0.57; 95% CI 0.51-0.64). This remained significant after controlling for a broad range of potential confounders including psychotropic co-prescription, symptom severity, functional status and hospital admissions (hazard ratio=0.77; 95% CI 0.67-0.87).

Conclusions: In a large cohort of patients with Alzheimer's disease, AChEI prescription was associated with reduced risk of death by more than 20% in adjusted models. This has implications for individual care planning and service development.

Keywords: Alzheimer's disease; Acetylcholinesterase inhibitors (AChEIs); Treatment effect; Survival; Predictors

Key points:

- Acetylcholinesterase inhibitor prescription is less likely in patients of higher age, lower MMSE, who are unmarried and from more deprived areas.
- Receipt of an acetylcholinesterase inhibitor was associated with reduced mortality in the whole sample by at least 20%.
- Findings were robust to adjustment for a large number of confounders and propensity scores.
- Greater survival benefits were detected in patients without hospital admission in the year prior to Alzheimer's disease diagnosis.

Introduction

Dementia is more frequently recorded on death certificates [1] and is now the leading reported cause of death for women in England and Wales [2]. Mean survival time with dementia varies between three to ten years [3], depending on study design but also potentially on dementia management. Acetylcholinesterase inhibitors (AChEIs) are established in dementia treatment, and continuous treatment into the moderate-to-severe stages of Alzheimer's disease (AD) is associated with cognitive and functional benefits, as well as independence and home living [4, 5]. However, concerns have been raised about the cardiac safety of these agents, as well as risks of falls and hospital visits due to syncope, bradycardia, pacemaker insertion and hip fracture [6, 7]. The extent to which these potential benefits and risks affect mortality remains unclear, as associations have been conflicting. While early evidence from randomised controlled trials [8], matched observational data [9], and a large cohort study [10], did not identify any association between AChEI use and mortality, more recent larger cohort studies [11,12] have reported improved survival, although study designs, cohorts and effect sizes have varied.

Our aim was therefore to investigate the association of AChEI receipt with mortality in a large, naturalistic sample of patients with clinically diagnosed AD, taking into account baseline functioning, mental and physical wellbeing, as well as using propensity scores to minimise potential confounding by indication.

Methods

Data source

Data for this study were obtained from the South London and Maudsley NHS Foundation Trust (SLaM) Clinical Record Interactive Search (CRIS) application. SLaM is one of Europe's largest healthcare providers for mental disorders and dementia, serving a geographic catchment of four South London boroughs (Lambeth, Lewisham, Southwark, and Croydon) with a population of over 1.2 million residents. SLaM provides specialist dementia assessment and care for all residents in the catchment areas, including those living in residential care and admitted to general hospitals. In 2007-8 the CRIS application was developed to provide research access to anonymised copies of SLaM's electronic health records within a robust governance framework [13, 14] including ethical approval as a data resource (Oxford Research Ethics Committee C, reference 08/H0606/71+5). CRIS has been linked to national data on hospitalisations (Hospital Episode Statistics; HES) and mortality which have permitted the analyses presented here.

Sample

CRIS was used to extract cases aged 65 years or older who received a first diagnosis of AD from SLaM services within the 4-year period between 1st Jan 2008 and 31st December 2012. Diagnoses are routinely coded using International Classification of Diseases, Tenth Revision (ICD-10) categories [15] and these stuctured data were supplemented by a bespoke natural language processing algorithm using General

Architecture for Text Engineering (GATE) software [16] which extracts diagnoses recorded in text fields [13, 16]. To minimise confounding morbidity, cases were excluded if the initial AD diagnosis was received from SLaM services providing liaison input to acute hospital inpatients, as were cases who died within 6 months of the first AD diagnosis.

Measurements

Demographic data were extracted from routinely completed fields and included age at AD diagnosis, gender, ethnicity (categorised into White-European and non-White) and marital status. Socioeconomic status was estimated from a neighbourhood-level index of multiple deprivation [17]. GATE-hosted applications were used to identify the following parameters from text fields [13], supplemented by information from structured fields when available: i) recorded prescription of AChEIs within 6 months of AD diagnosis (the primary exposure); ii) Mini-Mental State Examination (MMSE) [18] score closest to AD diagnosis; iii) recorded prescription of antipsychotic, antidepressant or hypnotic medication prior to AD diagnosis [13]. Data were also extracted from structured Health of the Nation Outcome Scales (HoNOS65+), routine measures of wellbeing used in UK mental health and dementia services [19]. Subscales on symptom severity and functional status were included in this analysis, using scores recorded closest to the AD diagnosis date. HoNOS65+ subscales are each rated 0 (no problem) to 4 (severe or very severe problem) which we dichotomised to ‘minor or no problem’ (0-1) and ‘mild to severe problems’ (2-4). From hospitalisations for physical disorders in the year prior to dementia diagnosis, the primary and first two secondary discharge diagnoses were extracted as indicators of

comorbidity. Mortality up to 22nd September 2015 was ascertained from linked national data and analysed as the primary outcome. Follow-up started 6 months after the AD diagnosis and ended either at death or the aforementioned censoring point.

Statistical analysis

STATA 13 software was used (Stata Corp LP, College Station, TX, USA). Patients prescribed AChEIs were compared to the remainder with respect to other covariates. Kaplan-Meier curves with log-rank tests were initially used to compare survival between exposure groups. Cox regression models were used to investigate associations between AChEI prescription and all-cause mortality. In order to separate the measurement of exposures/covariates and the ascertainment of outcome, the sample was restricted to survivors at 6 months after dementia diagnosis, and the exposure comprised AChEI receipt up to that point. To reduce confounding by indication we calculated and adjusted for a propensity score [20] representing the probability of being treated with an AChEI based on a regression model which included all the aforementioned covariates. The propensity score was included in a Cox model in place of these covariates, followed by an analysis restricting the sample to patients at risk of receiving AChEI based on their propensity score. We further established a case-control cohort by matching AChEI receivers and non-receivers on their exact MMSE score at dementia diagnosis.

Results

Population characteristics

We identified 3199 patients diagnosed with AD in the observation period. Patients who died within 6 months of diagnosis, patients under the age of 65, patients active to liaison psychiatry services at the time of AD diagnosis, and patients who received AChEIs but not within 6 months of AD diagnosis were excluded. This resulted in 2464 included patients with AD of whom 1220 (49.5%) died within the follow-up period. The mean (SD) follow-up time was 3.66 (1.69) years.

Of the 2464 cases at baseline, 1261 (51.2%) were prescribed AChEIs and characteristics of AChEI users and non-users are compared in Table 1. Of the 21 patient characteristics associated with not being prescribed AChEIs, 13 were also associated with higher mortality in age- and gender-adjusted models (Table 2). Factors associated with increased mortality in these models were: increased age, psychotropic medication use prior to AD diagnosis (antipsychotic or hypnotic/anxiolytic), agitated behaviour, hallucinations or delusions, physical illness or disability, activities of daily living impairment, impaired occupational/recreational activities, and all hospitalisation diagnoses apart from musculoskeletal and digestive system disorders. Factors associated with lower mortality were: female gender, non-White ethnicity and higher MMSE score. When all aforementioned covariates and AChEI prescription were entered into the same model, the following factors remained independently significant ($p<0.05$) covariates: age, gender, ethnicity, MMSE score,

physical illness or disability, impaired activities of daily living, and hospitalisations with cancer or genitourinary disease diagnoses.

After matching for exact MMSE scores, 953 patients remained in each group. Mean (SD) MMSE score was 19.8 (5.8), mean (SD) follow-up time 3.0 (1.7) years. Cohorts did not differ significantly in numbers of deaths and demographics (age, gender, ethnicity, marital status, deprivation score).

AChEIs and survival

Kaplan-Meier curves (Supplementary Figure 1) comparing survival between AChEI users and non-users indicated substantially lower mortality in those receiving this treatment (log-rank test; $p<0.01$). Further Cox regression models (Table 3) confirmed strong associations between AChEI prescription and reduced all-cause mortality which remained significant after adjusting for all covariates. The most substantial changes in the strength of association occurred following adjustment for age and gender, and then again following further adjustment for other demographic factors and cognitive function at baseline. Standard propensity scores were created using all variables from the fully adjusted model. For this analysis, 2143 patients lay within the region of common support (i.e. where there was substantial overlap between characteristics of treated and untreated groups) with propensity scores ranging between 0.101 to 0.895; of these, 1181 (55.1%) were prescribed AChEIs. In summary, hazard ratios remained virtually unchanged compared to the fully adjusted model. In the MMSE-matched sample, hazard ratio for death was 0.79 (95% CI 0.69-0.89) and thereby very similar to the fully adjusted model from the original cohort.

In further analysis we stratified the sample into two groups by the median MMSE, score but found no substantial difference in associations of interest in patients with milder cognitive impairment at diagnosis (MMSE≥21; age- and gender-adjusted HR=0.75; 95% CI 0.62-0.92) compared to those with worse cognitive scores (MMSE<21; age- and gender-adjusted HR=0.70; 95% CI 0.59-0.82). However, the association between AChEI prescription and lower mortality was more pronounced in patients who did not have a hospital admission in the year prior to AD diagnosis (HR=0.62; 95% CI 0.53-0.71) compared to those who did (HR=0.74; 95% CI 0.62-0.89; adjusted for age and gender).

Discussion

In our analysis of a large sample receiving routine assessment and care for AD, mortality was more than 40% reduced in those prescribed AChEIs. This association was attenuated to around 20%, but remained significant, after controlling for a broad range of confounders, including psychotropic prescription, mental health symptoms, general physical health, functional status and hospitalisations with physical illness in the year prior to dementia diagnosis. The group of patients not receiving AChEIs did have an adverse health and functional profile, with 13 of the 21 patient characteristics associated with non-prescription also significantly associated with higher mortality. However, our findings remained robust to cognitive score matching, propensity score adjustment, and sensitivity analyses to address potential bias by indication.

Our findings are consistent with some large scale cohort studies, which have reported lower mortality associated with AChEI use. Nordstrom and colleagues [11] followed 7073 patients on the Swedish Dementia Registry, of whom 5159 were prescribed AChEIs. After adjusting for demographic factors, residency, presence of a care package, cognitive and nutritional state, co-morbid cerebrovascular and cardiovascular disease, as well as certain medications (antihypertensives, antidiabetics, antidepressants, and neuroleptics) substantial reductions in myocardial infarctions (hazard ratio=0.62) and mortality (hazard ratio=0.64) were detected, which remained significant after matching for propensity scores. Similarly, a more recent study using Taiwan's National Health Insurance Research Database found that people with neurodegenerative dementia treated with any anti-dementia drug had comparable

survival to a group without dementia after adjusting for demographic factors, urbanicity and a physical health co-morbidity index [12]. However, the above studies were not able to fully account for psychotropic prescription, dementia subtype diagnosis, mental health symptoms, cognitive function at presentation, or a wider range of co-morbidities.

Although almost 50% of patients died within the follow-up period, survival time until death or censoring was within range of what is reported in the literature [3]. Our findings regarding other factors influencing mortality in dementia cohorts are in line with those from previous studies, including older age, male gender, worse cognitive impairment and worse functional abilities [10, 11, 21]. These remained significant in a fully adjusted model supporting the comparability of our findings. White ethnicity was independently associated with a higher mortality risk, which might possibly be viewed as unexpected, given levels of disadvantage experienced by minority ethnic groups; however, this observation is in line with previous research in this database and the United States [22, 23].

Although they cannot be inferred directly from our data, a number of factors are likely to underlie the observed prolonged survival. While these include the direct effect of AChEIs on cognition and functioning which might have a positive impact on survival [24, 25], AChEI use might possibly be a proxy marker for increased family involvement and requests for more assertive intervention in AD [24]. Indeed, in our sample people receiving AChEIs were more likely to be married and to be residing in wealthier neighbourhoods, and were less likely to have difficulties with living conditions or social relationships compared to AChEI non-users. However, the survival benefit associated

with AChEI prescription remained strong and statistically significant after adjustment for these factors. Of potential relevance, there is growing recognition of acetylcholine's widespread presence in the body [26] and its hypothetically beneficial role in the cardiovascular system, where vagotonic stimulation improves survival in heart failure in animal models [27]. Other studies have suggested that AChEIs have anti-inflammatory properties [28] and reduce markers of endothelial and platelet activation [29]. Hence Nordstrom and colleagues [11] speculated that AChEIs could influence plaque stability in atherosclerosis or improve cardiac function by reducing oxygen demands. This is further supported by the observation that higher doses of AChEIs appear to lead to better survival in patients with Alzheimer's disease [11], although we did not have sufficient data to test dose-response associations in our sample.

This study has a number of strengths. A large sample was analysed, drawn from a near-monopoly dementia assessment and care provider for an ethnically and socially diverse population, maximising the representativeness of the sample to its source population. We had sufficient statistical power to control for a range of potential confounding factors, which to our knowledge superseded those captured in any previous study of this scale. Our findings were additionally robust to a series of sensitivity analyses, including propensity score adjustments.

Limitations, however, include the fact that this was an observational study and therefore inevitably subject to residual confounding. Noticeable differences in baseline factors existed between AChEI user and non-users and it is likely that healthier patients were prescribed AChEIs more frequently. Although we used propensity scores to perform sensitivity analyses, confounding by indication can never be entirely

ruled out in an observational study. There might be further confounders we are not able to measure. Most notably, we did not have sufficient information to adjust for level of education, although it is worth bearing in mind that the index of neighbourhood-level socio-economic status was associated with likelihood of receiving AChEIs, but not with mortality. In addition, a number of prospective studies have not found any association between educational level and survival in AD [10, 21]. Symptom severity and functional status were ascertained through the HoNOS65+ scale, which is a widely used routine measure of clinical outcome in mental health and dementia services in the UK. It is important to recognise that its subscales are relatively brief measures and do not provide the level of detail that might be required for specific outcomes. Physical co-morbidity was primarily measured through linked data on hospitalisations which will only have captured severe disorders requiring inpatient care. Nevertheless, the British Hospital Episode Statistics database has been previously used to identify patient cohorts with certain characteristics with a high degree of accuracy and outcome prediction [30].

Conclusions

Our results suggest that people with AD who are prescribed AChEIs have reduced mortality by approximately 40%, half of which remained independent of a range of potential confounding factors. As this is a retrospective observational study, stronger evidence could be achieved through replicating these results in a randomized controlled trial or a prospective cohort study. However, as AChEIs are now established in clinical practice and generally well-tolerated, depriving patients of AChEI prescription would be considered unethical. Our findings have potential

relevance for patients and their families, as well as for clinicians and policymakers in evaluating post-diagnostic care, although generalisability and underlying processes require further evaluation.

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Author contributions: CM, GP and RS conceived the idea for this study and designed the analysis plan with input from all authors. CM and GP implemented the analysis plan, with input from RDH, HS and RS. The manuscript was drafted by CM with input by GP, RDH and RS. All authors read and approved the final manuscript.

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Tables

Table 1: Sample characteristics by AChEI status

Risk factors	AChEI non-receipt (n=1203)	AChEI receipt (n=1261)	P value*
Socio-demographic status and cognitive function†			
Mean age at dementia diagnosis (SD)	83.1 (7.0)	80.8 (6.6)	<0.01
Female gender (%)	66.2%	67.1%	0.63
Non-White ethnicity (%)	17.0%	19.4%	0.14
Married or cohabiting status (%)	30.6%	42.9%	<0.01
Mean index of deprivation (SD)	26.7 (13.0)	25.5 (12.6)	0.02
Mean MMSE score at diagnosis (SD)	17.8 (6.6)	20.1 (5.6)	<0.01
Psychotropic use prior to AD diagnosis (%)			
Antipsychotic	6.6%	5.1%	0.11
Antidepressant	13.7%	13.4%	0.82
Hypnotic/anxiolytic	6.2%	4.4%	<0.05
HoNOS65+ problem due to mental or physical symptoms (% with subscale scores 2-4)†			
Agitated behaviour	17.0%	10.9%	<0.01
Non-accidental self-injury	1.7%	0.5%	0.01
Problem-drinking or drug taking	2.8%	1.9%	0.13
Hallucinations or delusions	12.8%	8.2%	<0.01
Depressed mood	14.1%	10.7%	0.01
Physical illness or disability	49.0%	32.3%	<0.01
HoNOS65+ functional problem (% with subscale scores 2-4)†			
Activities of daily living (ADLs)	58.8%	42.6%	<0.01
Living conditions	11.6%	5.8%	<0.01
Occupational/recreational activities	31.8%	21.9%	<0.01
Social relationships	15.0%	10.9%	<0.01
Recent hospitalisation diagnosis (ICD-10 code) (%) – in the year prior to AD diagnosis			

Cancer (C00-C97)	2.5%	2.2%	0.66
Musculoskeletal illness (M00-M99)	8.4%	5.1%	<0.01
Metabolic illness (E00-E90)	11.4%	6.7%	<0.01
Respiratory illness (J00-J99)	9.4%	4.2%	<0.01
Digestive system disorder (K00-K93)	11.1%	7.9%	<0.01
Injury or poisoning (S00-T98)	12.1%	6.5%	<0.01
Genitourinary disease (N00-N99)	13.6%	7.1%	<0.01
Circulatory disease (I00-I99)	23.9%	15.4%	<0.01
Neurologic disease (G00-G99)	3.8%	4.3%	0.56

* independent samples t-test or chi^2 test
† at the time of AD diagnosis

Table 2: Unadjusted and adjusted analyses of associations between covariates and mortality after Alzheimer's disease diagnosis

Covariate status at/around diagnosis	Association with mortality – Hazard ratio (95% CI)	
	Unadjusted	Age and gender adjusted
Age (per year increment)	**1.08 (1.07-1.09)***	**1.08 (1.07-1.09)***
Female gender	**0.77 (0.68-0.86)***	**0.67 (0.60-0.75)***
Non-white ethnicity	**0.61 (0.51-0.72)***	**0.73 (0.62-0.87)***
Married or cohabiting status	1.12 (0.99-1.26)	1.03 (0.91-1.18)
Deprivation score (per SD increase)	1.02 (0.97-1.08)	1.04 (0.98-1.10)
MMSE score (per unit increment)	**0.96 (0.95-0.97)***	**0.96 (0.95-0.97)***
Psychotropic use prior to AD diagnosis		
Antipsychotic	1.09 (0.87-1.37)	**1.29 (1.03-1.63)***
Antidepressant	1.05 (0.89-1.23)	1.16 (0.99-1.37)
Hypnotic/anxiolytic	1.25 (0.99-1.58)	**1.28 (1.02-1.62)***
HoNOS65+ problem due to mental or physical symptoms		
Agitated behaviour	**1.29 (1.10-1.51)***	**1.32 (1.13-1.54)***
Non-accidental self-injury	1.20 (0.72-1.99)	0.89 (0.53-1.49)
Problem-drinking or drug taking	1.03 (0.70-1.52)	1.26 (0.85-1.87)
Hallucinations or delusions	**1.22 (1.02-1.46)***	**1.30 (1.09-1.55)***
Depressed mood	0.98 (0.82-1.17)	1.06 (0.89-1.27)
Physical illness or disability	**1.74 (1.55-1.95)***	**1.52 (1.36-1.71)***
HoNOS65+ functional problem		
Activities of daily living (ADLs)	**1.66 (1.48-1.86)***	**1.55 (1.38-1.74)***
Living conditions	**1.25 (1.03-1.52)***	1.20 (0.99-1.45)
Occupational/recreational activities	**1.33 (1.17-1.51)***	**1.34 (1.18-1.51)***
Social relationships	0.96 (0.81-1.14)	1.08 (0.92-1.29)
Recent hospitalisation diagnosis (ICD-10 code) – in the year prior to AD diagnosis		
Cancer (C00-C99)	**1.84 (1.33-2.55)***	**1.65 (1.19-2.29)***
Musculoskeletal illness (M00-M99)	1.09 (0.88-1.37)	1.01 (0.80-1.26)

Metabolic illness (E00-E99)	**1.38 (1.15-1.66)***	**1.30 (1.08-1.56)***
Respiratory illness (J00-J99)	**1.54 (1.26-1.89)***	**1.42 (1.15-1.74)***
Digestive system disorder (K00-K99)	1.15 (0.96-1.39)	1.09 (0.91-1.31)
Injury or poisoning (S00-T99)	**1.53 (1.28-1.82)***	**1.25 (1.05-1.49)***
Genitourinary disease (N00-N99)	**1.75 (1.48-2.06)***	**1.46 (1.24-1.73)***
Circulatory disease (I00-I99)	**1.43 (1.26-1.65)***	**1.23 (1.08-1.41)***
Neurologic disease (G00-G99)	**1.54 (1.19-1.97)***	**1.67 (1.29-2.15)***

* $p<0.05$

Table 3: Multivariate Cox regression analyses of association between receiving AChEI treatment and all-cause mortality in individuals with Alzheimer's disease. 2464 cases. 1220 deaths.

Prescribed AChEI	Hazard ratio (95% CI)
Crude	**0.57 (0.51-0.64)***
Adjusted for age and gender	**0.65 (0.58-0.73)***
Adjusted for all demographics	**0.65 (0.58-0.74)***
Adjusted for demographics and cognitive scores	**0.73 (0.64-0.83)***
Adjusted for demographics, cognitive scores, and psychotropic prescription	**0.73 (0.64-0.83)***
Adjusted for demographics, cognitive and HoNOS65+ scores	**0.76 (0.67-0.87)***
Adjusted for demographics, cognitive scores, and hospital episode statistics	**0.75 (0.66-0.85)***
Fully adjusted (all of above)	**0.77 (0.67-0.88)***
Adjusted using propensity score as a covariate	**0.78 (0.68-0.89)***
Fully adjusted including those at risk of being treated with AChEI	**0.77 (0.67-0.87)***

* $p<0.05$

Supplementary Figure

Figure 1: Kaplan-Meier curves displaying the survival status of Alzheimer's disease patients comparing those who received AChEIs and those who did not (n=2464); 95% confidence interval